Parasite

Plasmodium falciparum histidine-rich protein 2 and 3 deletions: mechanism, impact, and consequences

Many malaria Rapid Diagnostic Tests (mRDTs) are based on the detection of the HRP2 protein in the malaria parasite. *Plasmodium falciparum* with histidine-rich protein gene *(hrp2/3)* deletions have emerged globally which has significant implications for the sensitivity of malaria RDTs. The deletions also affect the genomic structure of the parasites, which may impact parasite fitness and onward transmission.

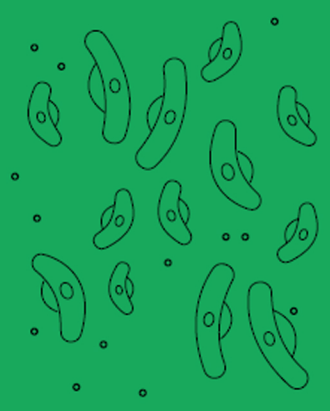
Collaborative LSHTM research helped develop an effective molecular tool to detect *hrp2/3* deletions in malaria parasites and conducted surveillance to identify the presence of parasites with these deletions in Somalia, Kenya, Tanzania, Yemen, Nigeria and other African countries, as well as in UK travellers.

Using the new tool, *hrp2/3*-deleted parasites were identified in several African countries and the tool has been supporting WHO-sponsored surveillance efforts. *hrp2/3*-deleted *P. falciparum* clinical isolates have successfully been culture-adapted, which helps understand the consequences of deletions and facilitates generation of high-quality genomic data. Thus far, more than 200 genes deleted together with *hrp2/3* have been identified.

These findings contributed to the implementation of country-wide systematic surveillance of *hrp2/3* deletions in malaria parasites in several African countries, providing vital information for malaria diagnostic policy.

Single dose Tafenoquine to stop human-to-mosquito transmission

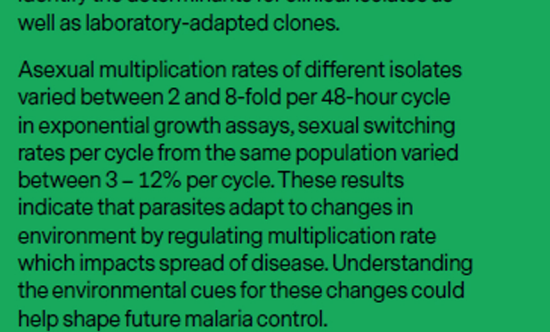
Standard antimalarial therapies are effective at killing disease-causing blood stage malaria parasites, but have limited impact on gametocytes, the stages transmitted from humans to mosquitoes. A single low dose of a drug like primaquine can entirely stop transmission, but primaquine is only active for a matter of hours. Tafenoquine (TQ) has a far longer half-life, yet its efficacy as a transmission blocker for *P. falciparum* in humans had never been tested.



Together with collaborators, LSHTM teams conducted a clinical trial in Ouelessebougou, Mali, to test the transmission blocking activity of TQ, in combination with standard artemisinin combination therapy (ACT). Transmission was assessed using direct membrane feeding assays, in which blood from the malaria positive recruits was provided to mosquitoes in a heated glass apparatus.

Malaria transmission stopped more rapidly in all TQ treatment groups compared to the ACT only control. In the highest TQ dose group, transmission completely stopped between 3-7 days post-treatment, whereas in the ACT-only group, transmission was observed until the end of measurements at day 14. Subsequent trials demonstrated the transmission reducing effect occurs at 3-5 days post treatment.

These results indicate that single low doses of TQ are effective in reducing transmission of *P. falciparum* in humans; future trials must demonstrate whether this effect is long lasting.



Scientific section - A snapshot of projects focusing on the parasite

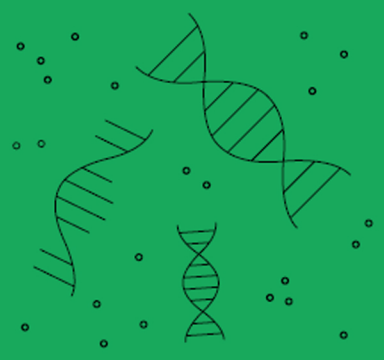
Monitoring markers of antimalarial resistance using genomic surveillance

Malaria parasites have developed resistance to artemisinin combination therapies in Southeast Asia- with signs that this is now also occurring across Africa. This project identifies genomic DNA and RNA markers of antimalarial resistance, which are used to develop genomic surveillance panels for African malaria parasite populations.

This vital research, taking place in The Gambia, Senegal, Ghana, and Nigeria, has built capacity for and is generating data on *in vitro* antimalarial susceptibility testing of malaria parasites across these countries. Tested parasite isolate genomes and transcriptomes are then generated to determine genetic variants and pathways modulating differences in response to antimalarial drugs.

Comparable and reproducible *in vitro* antimalarial sensitivity test results are now possible from Ghana, The Gambia, and Nigeria, while Senegal is developing the infrastructure for testing. Pilot genome-wide association analysis revealed multi-linked genomic interactions that correlate with *in vitro* drug responses. These markers are being surveyed in natural populations, with over 1000 genomes of *P. falciparum* from Nigeria already analysed.

This project enables comparable assessment of antimalarial susceptibility and molecular surveillance between regional laboratories, improving the monitoring of current antimalarial drugs across Africa.



Shapeshifters - Adaptive variation in malaria parasites

Understanding how pathogens survive and reproduce in different environments should guide implementation of available control methods and help elimination strategies. This is particularly important for the natural variation in asexual and sexual replication rates of malaria parasites, which affect how easily the disease is transmitted.

Together with collaborators, LSHTM teams investigated the multiplication rate variation for parasites from different endemic populations. *P. falciparum* parasites also exhibit naturally occurring switch rates to sexual differentiation per asexual cycle. Both were monitored to identify the determinants for clinical isolates as well as laboratory-adapted clones.

Asexual multiplication rates of different isolates varied between 2 and 8-fold per 48-hour cycle in exponential growth assays, sexual switching rates per cycle from the same population varied between 3 – 12% per cycle. These results indicate that parasites adapt to changes in environment by regulating multiplication rate which impacts spread of disease. Understanding the environmental cues for these changes could help shape future malaria control.

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